Lysergamide

Synthesis

Demystified

Michael

Yost

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LYSERGAMIDE SYNTHESIS DEMYSTIFIED
Michael Yost

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Lysergamide synthesis has been obfuscated, for a variety of reasons, and kept from the public for far too long. A book like this is long overdue, and after this book gets in the hands of the reading public, no doubt others will make even better books, once the ice is broken. The secrets of the field have been kept hidden, and taught only to those who go off to advanced chemistry schools, pharmacology, medicinal chemistry, etc. where the uninitiated get revealed to them how to make items in this category by the initiated. Seldom has anyone revealed those secret details applied to this, but this book will reveal the magic act behind the scenes once and for all, and those with curiosity on the topic will be satisfied about the topic.

Books have hinted at the various issues, without the implications of what they were parroting and regurgitating sinking in. I quote from the first LSD manufacturing case, ironically, before it was even made illegal and most had never heard of it before: I have already invested a year - on and off - and all the money I could save on this project, and I was at the point of admitting defeat. At this time, I was naturally reading everything I could lay my hands upon about ergot alkaloids. I stumbled upon a few articles that at first seemed quite unrelated to LSD, but they were logical and worth a try; because by comparison the process was exceedingly simple, compared to Hofmann's monumental preparation."If you want to read an interesting legal case - without proof, and without a jury, the government merely asserted he had taken it to Canada and brought it back to violate an importing label requirement while the government had several federal agents across the country following him around trying to bust him.

> Now from Scully:
> “What were some things they taught you, some “tricks of the trade”? “Bear was obsessed with purity and yield. The overwhelming majority of what he taught me was basically lab technique and how to handle … So by the time I hooked up with Bear I had a rough idea from the published literature, What I learned eventually is that that’s just a drop in the bucket. Really, the information you need for making LSD is mostly lab technique and tricks of the trade. Lysergic acid compounds are very fragile, and they have to be handled with much more care than many chemists would believe." - Scully The issue is

many fold, but it boils down to alkaloids. Caffeine is extracted from bean, and you notice in a few hours it is not as fresh as it was afew hours before, The lysergic skeleton has tremendous ring strain, due to bonding angles, and the top ring has that nitrogen, which if you look at it, is basically a Hunig’s base variation (an unusually strong base) attached to the indole.

As Shulgin says, at least as far as a chemist would know, as a salt it is stable. But as a base, it is an air sensitive molecule, which means air sensitive techniques must be employed to protect it from damage. Not only is it subject to that, it is subject to that very quickly. In this book I will show ways to improvise these procedures in detail, applying them to a particular synthesis. Be warned, the inert gas you use has to be high purity chemistry grade gas. Also, sources of alkaloids will be presented, and various amines. Many of the various synthesis require water content to be drastically reduced to a few parts per million to work, so drying tech will be presented for those. There are reactions that are even more water sensitive than that, but that won't be needed for this. Protection and care must be taken when working around ergot alkaloids, as I surmise Hoffman figured 50 mg of starting material wouldn't be enough exposure to affect him when he went to make it and got a brief tinge of effect. Respirator mask, ear, eye, skin etc. have to be protected when working around these molecules. Disclaimer: see Legalese chapter.CHAPTER ONE THE SHULGIN SYNTHESIS The first step of clandestine lysergamide synthesis typically is the hydrolysis of an ergot alkaloid, You add water, under alkaline or basic conditions to liberate the acid and amine from an amide. The second step would be to join the lysergic portion, usually via intermediate, back with an amine to form an amide, for instance diethylamine.

Now in this first step of the synthesis, one of the sections of the lysergic molecule’s stability comes into play. The double bond in the top ring is in jeopardy, as the reaction is done in water that can add across it in presence of light and acidic conditions later on. The answer for that is quite simple, low wattage lighting; a dimmer switch can achieve this, keeping lights low to a minimum, and if you have available a red or yellow (not orange) photographic safelight, that could be used if the wattage is kept low, way below 15 watts. At certain points wrapping things in a few layers of aluminum foil will further keep the exposure to light to a minimum. The biggest and far bigger concern is the fact you had an ergot alkaloid salt, and alkaline conditions will freebase the alkaloid in solution, and surface contact in the process of time will destroy and ruin it unless an inert gas covers the top of the solution. There is an error Shulgin gives, and it keeps people from knowing about the problem, and figuring it out. He claims he makes lysergic acid hydrate, But if you look, what it actually makes is lysergic acid hydrate, sulfate salt. Another part he is actually isomerizing the lysergic all to the regular form, but I will advise for reasons to leave the lysergic acid isomerically mixed at that point.Now your inertness must be addressed. You have your cylinder with your regulator etc. Again it must have a slightly positive pressure. You are going to be attaching it as an inlet via syringe. You may think this unneeded, at this stage, but the reason will become apparent as you progress through the steps and procedures and syntheses. So you might as well get used to doing it this way, as you will see. A connector, usually from Luer lock for needle to gas tubing is in order. The only other way I know would be to find a glass syringe/ needle combo that you can remove the plunger and break the back part in some way to attach your gas tubing, possibly clamping it, that is around the diameter of your gas line. If you read about Schlenk techniques, you will see about their set up, dual manifolds etc. You will need multiple sources of gas inlets for the procedures, so be ready for that fact, of needing multiple inert gas lines simultaneously. To add your two first ingredients, KOH, and ergot alkaloid salt (a tripeptide), you will put them in distilled water and transfer them in with stirring. Half the KOH he calls for in 50 ml water, and your alkaloid salt in 25 ml water, you can add the alkaloid first. Once both are added, add the amount of KOH in 12.5 ml of water and add slower than the first addition, then the rest in the other 12.5 ml, slightly slower than the previous addition, That can be done with a syringe, or something called cannula, essentially a double ended needle, which will be described to you for the second step.

You need to have a magnetic stirrer. Your reaction vessel has to have an addition funnel, and a septum on the necks. The easiest is Teflon sleeves for your ground glass joints, but if all you have is Teflon tape, you wrap it around the bottom of the male joint, and work your way up, then snug them together. This creates a gas tight seal.

You can either flush the flask for some time with your inert gas, or if you attach your vacuum that uses a needle to another septum on the other neck, you can fill, purge and refill several cycles. When you need to vent, you merely insert a plain needle through the septum to maintain normal pressure. You want to re-use the same places you insert your needles, time and time again, to not wear out your septum. Remember your gas has to have a slightly positive pressure. Even better, to get you trained, for what is coming, is to put a septum on top of your addition funnel and run inertness in there also. Doing this set up in a fume hood is a plus, if not you may have to vent out of the reaction vessel into another container with either acids or bases, bubbling it in to trap certain chemicals for some reactions, So once you have good inertness going in your items you prepared, and you have addedyour ingredients, and you have the temperature right, and you have it going for the four hours he calls for at 75 C - which you can cut the lights off entirely if not concerned about it or wrap it in layers of foil as best you can - then you can add your sulfuric to your addition funnel with no worries at this point, and then add your dilute sulfuric slowly with stirring, after it being for sure cooled way down first, down to he says around a pH of 3 or so, which he was really pushing it pretty close to danger zone; I would suggest babying it at 3.5 to 4 pH, if you can get the same results close in yield to what he did, you are going to remove any needles still in the septum in the proper sequence, make sure it is wrapped in foil good and shove it in the fridge for the night. Okay, recall now you need to be mindful of the lighting situation. Your blacklight should also be kept to minimal exposure when used sparingly, and if possible lower wattage than typical, perhaps a cord that can turn down the juice would assist. At RT, in acidic water, with normal UV blacklight wattage, blacklight shining continuously, the fluorescence starts fading and goes away completely in about 4 minutes, so be careful. Remember water or alcohol, in UV light or regular light, especially in acidic conditions can add across the double bond. So you keep any lighting dim, very low. Now your eyesight might go bad like that, but every profession has its hazards, I suppose, Assuming you had the correct items to start with and followed the procedures so far, you have your lysergic acid hydrate sulfate sitting in your cold fridge forming some crystals, but it needs to be cleaned up. Since you got acidic water, and you need to filter, you need special filter paper to do the job. You require unfolded glass fibre filter paper, and you have to have some pure ether to do the washing. This first part was nowhere near as complex as what is coming, so relax and do the filtering and washing. I have heard ether can be gotten from sodium ethoxide and ethyl bromide or iodide, but who knows, right? If you have never done a filtering, you carefully pour it into your funnel for filtering, this filtering is done flat, so it might be called a Buchner funnel, and if you wash, sometimes you need to be careful when doing so, I don’t know if this is one of those, but he does not seem to state to do it sparingly or anything. So what he is doing is filtering out at the next step the potassium sulfate, but since he is using anhydrous ammonia in ethanol, that will convert iso to regular. Now I mentioned not to do this earlier and I will explain why here. The method he uses pocl3 if done correctly will result in littleto no iso formation, so at this step he converts it. The problem though is this, you currently have a salt which is safer to handle and work with; normally the stronger acid will be attracted to the stronger base; however, ammonia sulfate will precipitate from absolute ethanol; I do not know if he is freebasing it or not while doing this, so to be on the safe side, I say just filter out the potassium sulfate and leave it isomerically mixed so it is still a salt. 1 could show you just in case how to do it his way, but if you read this book completely, you will know how to anyway if that is what you decide as a serious experimenter, instead of just an topical information interest curiosity person, or just a reader, as most if not all of you are, So you soak it in absolute ethanol twice and decant. I will show at the end of this chapter how to dry and transfer solvents. The ethanol filtering can be done with regular filter paper and filter funnel, so take your round filter paper, fold it in half, fold it in half again and open it to resemble the shape of a funnel and place it in the funnel. Use cold alcohol to wet the filter paper, and pour it in. Do not let your solvent go above the top of filter paper, wait until it goes down to add more solvent. If you are working in a high humidity area, which you shouldn't be, either move to anon humid area, or use several dehumidifiers in the room or rooms you are working. If not you have to use inertness containers to even do your dry alcohol step, but why create extra work for yourself? If you read this book entirely, you will know how to do dry inertness for your simple alcohol process here. When you get to the anhydride chapter, I explain why you only have to do this dry alcohol soak once. You will know how to do this with inertness if you find you want to, to filter out that K Sulfate. Okay you are ready to do the last part of his first step. Here he is adding something that will aid in salting out the lysergic sulfate, the ammonia will make ammonium sulfate. So we are going to have to follow his recipe to get it right, that means more inertness stuff (oh no!), This is just to be safe, as the solvent is water and ammonia is a weak base, and the sulfate should still be attracted to the stronger lysergic nitrogen in the top ring, but better safe than sorry I say. So your ethanol was put back in your prepared container, you removed the ethanol with vacuum, your inertness and addition funnel are ready to go to add your ammonia water and here you go! Cool it down and add your sulfuric slowly with stirring and send it to the fridge again and filter with the proper filter paper and wash it until the lysergic acid hydrate sulfate looks nice, then you can dry it.The second step is very tedious and complex including the cleanup. But after I explain this, you will probably think it has spun you for a loop. But I assure you this is how you have to do these types of things. First, this reaction is water sensitive. Your reagent is dangerous, but because it is water sensitive, it will work with the monohydrate. Before I show you how to prepare for this, I have to teach you one concept, a concept you will use over and over so much you can do most things with this one technique, The reagent from industry comes in a sure seal bottle, meaning able to be pierced by a needle, and in theory a needle will transfer an exact amount or close to it, but it would take a Teflon plunger type needle glass syringe which is pricey and you have to use Vaseline to seal it gas tight and itis really advanced stuff, so I will teach you this safer method, and you may have to ballpark the amount, and you may have some left over you have to neutralize, but for a newbie, it will be safer, and you really should be doing this in a fume hood just in case, as this molecule is similar to those that give people gulf war illness, And you certainly shouldn't be doing things like this anyway. The technique is called cannula transfer. Back in the 70s, when you were short on gasoline money, people used to siphon gas out of their neighbor's cars. You are going to be doing the reverse, using pressure to move things between your inert containers. So you have your inert gas set to slightly positive pressure, you will use a cannula, which is essentially a 2 or 3 foot flexible needle to puncture the septum and the container you want to transfer to has a needle to vent (a bleed needle) so things flow through the needle/cannula from your other container which is at positive pressure. Both have inertness going in, but the one you want things to go to has the needle bleed in it. Usually you insert the needle (cannula) in one of them just far enough to get the inert gas flowing, usually for 15 to 20 seconds, and then puncture through the septum of the other one. Then you lower it into what you want to transfer and voila! When enough has flowed you pull the needle up to the inertness level, not pulling it fully out to allow any residual in the needle to continue to flow. You should get some practice getting the positive pressure set right on your lines, and doing these transfers. You will then see several applications of this for working with the molecules allowing you to carry out the various syntheses and processes. Your glassware needs to be dry; your addition funnel cannot have a pressure equalizing arm, or if it does, you need to have a decent stopcock in the side arm as you need the pressure to be different at times to do it this way. And when you prep the glassware the way I show you with a seal of Teflon, your brief flaming, very brief, should not exceed Teflon’s 500 F temp issue. If you have an issue with the brief flaming, which you shouldn't, you need to do the reaction in the flask, and set up a separate addition flask and reaction flask vessel, but that brief flame time should not melt your Teflon or fuse your addition funnel. Your long needle

(cannula) has to be very flexible, as some are more rigid; you need the more flexible type, they certainly have them. To transfer in your lysergic, you will need to use a solvent, appropriately dried, as shown near the end of this chapter; in dried alcohol if the salt, in pyridine in a base,
You will need the monohydrate which means you have to heat it to drive off excess hydrates formed, even under vacuum to assist. So you can transfer in your solvent and then if in a different container, then into your reaction vessel once cooled. You had to be running your inertness with flushing or purge refill cycles obviously. The solvent to use in what I describe here will not be chloroform. Learning the quirks and issues with each solvent you may be interacting with is vital, as none of them are water, except water of course. Chloroform has its own issues, even though it may be trivial to have, there are a variety of reasons not to mess with it. The biggest reason for this is that the solvent recommended possesses the capability of drying to the level required for success easily. Because it boils at a lower temp, you need to run the reaction for a few more minutes. That solvent is DCM. So you got your reaction vessel prepared, you transferred in your lysergic and you removed the solvent you used to transfer it. Now you added your DCM. You got your stirring whizzing around. Now there are a few ways to get your pocl3 in. Obviously if you had a glovebox to get it started that would be a thing, but I presume you do not have one. One way is the Teflon plunger glass syringe with the Vaseline seal, but no on that for you, another way is to transfer from the container having your pocl3 into a container on top of a scale to get exact weight before transfer into your addition funnel, or the ballpark method of putting your cannula needle into your addition funnel septum and letting the inert gas flow for 15 or 20 seconds and then putting it into your bottle of chemical. Then lowering it slightly to get it started, and pulling it up slightly to complete theflow. You may not want to use the needle bleed for the flow for this, but more pressure slightly from where you are transferring it from. You need to insert your inertness in your pocl3 container first. I don’t know what he calls for, but it might be around 2ml, check online for TIHKAL 26 to see the recipe he gives. Check the density of pocl3 to see how many ml you would need. If when the time comes to drip you have extra, do not fret you will decompose and get it out of there when the time comes. That length of needle may be close to exact, so once you see the first flow show up, pull up slightly. If you accidentally add slightly too much, it is okay, within reason, as it will only serve to dry things more as it reacts with any minute amount of water that will hardly be there if you followed the advice I gave to get things prepped. If so, just add a little more amine to compensate, If you do things enough times, you will get it to exact enough no doubt. He calls for around 7 minutes of boiling, so because the temp is less with DCM, approx. 4 times that amount, or 28 minutes, let us say 30. While dripping it in, prepare the amine you have selected and get ready to transfer in, and you can go ahead and start transferring it, you should know how. Okay, around this time you are ready for your ammonia water. If you had any residual pocl3 in the addition funnel, you can decompose it with the ammonia water and transfer it out of there to another container that has either more ammonia or a strong base like KOH, to make sure it gets broken down, this dangerous stuff. Don’t forget DCM itself can also be dangerous as a solvent. So once your addition funnel is ready, insert your ammonia water and add it to your reaction flask, and make sure you spin your stirring bar strongly, and leave it stirring for a while, More stirring, Stir it real good. Then turn off the stirring, We are getting it all in one shot, instead of smaller amounts multiple times. It works. And now one of the big tricks. You transfer from your reaction vessel, into your addition funnel. When the layers separate, you lower the lower layer back into your reaction vessel. Voila! For the fabled scale up beyond this level of benchtop reactions, you have to go sideways first into a prepared flask, and then elevate it to transfer it back to your addition funnel, as there is a limit with a two or three foot cannula going uphill with slight positive pressure, for you scale up warriors I hear about. Those might be able to use the pressure equalizing funnel.Your addition funnel needs to have that ammonia water junk transferred out of there, perhaps even to your ‘any excess of pocl3’ container. And now you have to get your next trick ready. You are going to pull it out of your reaction vessel into a prepared container that has magnesium sulfate to dry your DCM, but you have to prepare your needle cannula special so you don’t draw any

solid into it when taking it back out. Take a cannula and around an inch or so from the end wrap some Teflon tape around it.

Now you need to have some small circular filter paper around an inch or so, Fold it in half and half again and put it on the end near the Teflon tape. Now Teflon tape it to secure it, not to cover the end of the needle with tape, but going back to the existing tape, securing the filter paper to the cannula needle. Place the other end up through the bottom of a septum and pull it through, so the filtered end would be inside the container you attach the septum to, for filtering. Prepare it with inertness with your magnesium sulfate and the other end can go into a container flushed out with inertness, or purged and refilled to set, without a bleed needle to remain at the same pressure while waiting. Do not do it the lazy way, of stuffing the other end of the needle part way in a septum to block it. Now you will transfer your DCM with your freebase alkaloid into that container with a cannula transfer to dry that solvent that just had contact with the ammonia water. When ready, use your filtered cannula to draw your DCM with alkaloid to the next container you will use, your 'removing the DCM' container. You need to remove your DCM, and if a dialkyl amine was attached, it is carefully important to not heat it up too much at all at this point. A rotary evaporator would be a nice Christmas present, but forget it. Your next option would be to have a dry ice acetone cold trap or two in your vacuum line, but you probably won't do that, at least not initially despite its ease. DCM, with some good stirring, and a little vacuum, possibly with a wee bit of heat will distill easily if you had that cold trap or traps. If not, you have to learn something called a vacuum distillation. You cannot dump DCM down the drain, as it will be in the water supply - that is a big no no. Remember to pull your vacuum needle out before turning off your vacuum, Magnetic stirring prevents DCM from bumping. Whatever you decide to get the solvent away from your amide, the next two steps are purification and salt formation. Shulgin mentions chromatography, but since you don't have fancy stuff like HPLC with inertness thrown in on the house and other niceties of a real lab, you are going to doa fractional crystallization at this step. Luckily he mentions a solvent, but because you had some iso in my advice I gave at least at this point, some matters must be addressed. I will provide info on a method adapted from Chinese herbalists when working with alkaloids, that of working with a salt for a column separation, but for now I will recommend the crystallization method at this point for this.He mentions benzene, luckily for you, a named solvent. Very likely hexane may also work. Don't know about toluene, You are going to transfer in your hot solvent to just dissolve it, and let it cool, and then cool it some more, You should go and learn about recrystallization techniques if you do not understand this part. Benzene's boiling point is rather close to the melting point of the dialkyl amide, so do not heat it all the way to boiling, hexane which very, very likely will substitute, has a lower BP, so you can use that hot, but again does not have to be at its boiling point either. The issue is that the iso may stay in the solvent, so when you go to cannula filter it, make sure you put it into a good inert vessel you transfer to, At this point, you can briefly check the theory with your low wattage dim UV blacklight to check. If there is enough fluorescence, that would be your iso. There would still be some iso in your product anyway, s0 it is okay, Once you have finished your crystallization and cannula filtering, add hot dry methanol with tartaric acid in it, and let it cool slowly, add ether to it, then shove it in the fridge wrapped in foil. Remember to always use dim lighting, Remember to let that one set a while in the fridge to fully crystallize out. When you do your filtering (with cold methanol to make the filter paper stick good), then washing, doing it carefully, babying it, then with a cold mixture of ether and methanol. You can then recrystallize. Now about this Chinese method for serious experimenters. You can use a column for salt chromatography. Use alcohol for the solvent. As long as you don't have excess acid in whatever you are shoving down the column, a little UV light ever so briefly to spot it moving. The issue with that is having particle sizes between certain sizes and roughly uniform for the medium you are using, there are different things one can use. The slurry method seems to gain favor for ease of packing the burette, the bottom has to have some stuff to keep the whole thing from falling out, cotton, filter paper etc. Your medium goes slightly more than half way up, and the solvent at the top needs to be occasionally replenished, as you drip the solvent through by gravity.

Once the iso is converted, you can recrystallize from benzene or hexane if desired prior to salt formation. The iso issue will be treated in a separate chapter, and now it is on to the part showing how to dry solvents, and some more advanced comments about the method in this chapter itself, to finish this chapter, so stay tuned, Sandoz is coming up next.If you have a vacuum desiccator and are in low level humidity conditions, this is far simpler to prepare your glassware for drying solvents, and is aplus, My guess is some don't have such things, so some more drastic actions will have to be employed to allow the drying to get to levels you need and require for some of these steps and procedures and syntheses. So you are going to cannibalize a distillation unit to get it to work. Assemble the pieces and you are going to flame it severely at every nook and cranny to fuse it together, and allow it to cool. Wrap Teflon tape outside before the joint and wrap it across the entire joint good to the other side. Attach your septum to each opening neck you have, and you are going to run and flush inertness through the whole thing good, and or purge refill to make sure you got a really good seal on it. Then it comes down to which solvent you need to prepare to be dry and which drying agents you need to do so. The procedure is to use strong magnetic stirring for about 3 or 4 hours with your drying agent and then distilling it to collect it, to transfer into your prepared inertness container, usually a septum attached flask for storage of your solvent getting ready to use it. For alcohol, usually gobs of ethanol molecular sieves do the trick once dried to a high level first. For things like amines, strong bases usually that absorb water are the first step if a particular synth needs it more as some dry during the reaction; a sodium second drying may be in order for others. You do not need to use a third stage, like sodium hydride, as that would be overkill for these syntheses. If you do not want to destroy your distillation unit to only do this, then you might try cannula transfer out for each succeeding stage if you are an experimenter type. If you are not wanting to do stirring on your DCM which dries it faster and you are patient, the alcohol molecular sieves in 12 hours will dry it to below levels needed for success.

For a more advanced procedure that should work, phosphorus pentachloride and DCM, can be added instead of pocl3, as it is water sensitive,and will react with the monohydrate to form pocl3 in the reaction vessel. This may be easier to obtain or work with, rather than trying to make something similar to a chemical weapon in your neighborhood. If you research and think you are capable, which you most likely aren't, you would need to ozonate at a certain step to complete the synthesis to high yields, as some methods to synthesize pocl3 leave that step out. Your needle cannula needs to be prepared by putting in a Pyrex dish and heating in an oven for a while, and to clean after transfers, run acetone through them, and more inertness to dry.Having sought out to trace this method from Tihkal, it turns out that this recipe was a variation from published literature given to Shulgin, with some suggestions from others, and he never actually did this. This hodegpodge may explain a few things unusual about it. Turns out, your amine needs to be dissolved in the solvent you are using, DCM, prior to addition.

Also, chapter 2 based on sandoz patents indicates it makes active product; unfortunately, since you started with iso, that is carried all the way through. If wanted you can epimerize the iso hydrazide at that stage, or just wait until completed fully to do so.

CHAPTER 2 SANDOZ To start out on this one with an opening salvo, it is ridiculously ludicrous to think or suggest people are going to work around anhydrous hydrazine. The Sandoz patents clearly indicate an alternative method, which of course will be employed in this chapter, as it is far safer and easier to work with without destroying either the place you are at or your own organs you need to survive and stay alive. The patent was an improvement on the old hydrazine hydrate method that yielded racemic products. I will mention that one at a certain point, but let us focus on this improvement, It uses an acid to form the hydrazinium ion, which does the reaction, on some things to extremely high yield, with the only downside being it forms almost exclusively iso product.

So you need your tripeptide base (in theory non tripeptides can be used, but the procedure is different, slightly longer, and lower yield) and then you need your hydrazine salt to have a higher molar ratio, more moles of your hydrazine salt to your ergot alkaloid base, and your acid has to have one hydrogen as the acid. Typically, people have hydrazine sulfate, but that has two protons. Sandoz most likely worked with the mono hydrochloride, but since you can't just buy anything these days, and that is harder to try to get right, we are left with something that fortunately can be made easily and purified to high levels. Hydrazine sulfate and sodium acetate in the minimal amount of water, and then you are going to flame heat it to get the displacement to occur to make sodium sulfate and hydrazine acetate. The sulfate is insoluble in methanol, and the acetate is solvated. You can then recrystallize. Anotherway if you have hydrazine hydrate and glacial acetic acid one to one just mix them together and it forms easily, Use alcohol to crystallize, and X- ray crystallography shows it to be exceedingly pure.

Now because you have your alkaloid base, and your hydrazine is in safer salt form, you need a solvent to do the reaction in, 1 propanol or 1 butanol are very close for BP to work, and are preferred. A glycol will also work, but you may want or have to distill later to remove for the cleanup, and those have high boiling points, But luckily, the hydrazide is one of the rare exceptions in these alkaloids and has a really high melting point, but the lower boiling point alcohols are the one you really prefer. In a subsequent chapter I show how to get to work with the freebase alkaloid to start, so do your preparation on your stuff to work with dry inertness. The cleanup involves removing your alcohol first. You are going to use ammonia water and DCM to separate. So you distill off your alcohol and then add ammonia water and DCM. Stir good, then you send and separate your stuff in your addition funnel, by the positive pressure method cannula transfer method I showed in chapter 1, and lower your DCM back into your flask.

Hot methanol added, any small amount of regular won't dissolve, the iso product which is most of it dissolves. The methanol being filtered by filter cannula transfer is to be removed which will leave your iso d lysergic hydrazide base to be ready to be treated to the hydrochloride salt for the next step, as both ways require it to be in that salt form, and both steps are done with water in the mix. This method is based on examples and combinations of the examples in the patent. It shows exact amounts to carry this out. If you want to recrystallize at this point, which is optional,for the freebase, the solvent is dry alcohol. Now the other older method with hydrazine hydrate, you simply heat it for a long time in the hydrate, once the hydrazide forms it precipitates out, in the racemic form, Guess how you isolate.

So, one method Sandoz patented for the next step essentially builds a coupling agent right onto the hydrazide to build a nice ring, a dimethylpyrazole right onto it. The other way proceeds through the azide.The pyrazole method uses some water, and some more hydrochloric acid, this of course threatens the double bond sufficiently enough that the Sandoz patent uses glyme, instead of the other examples without the double bond using ethanol. A small cyclic ether may also substitute. So you can already see your extremely dim light needs to be even dimmer if not off entirely, and your reaction vessel wrapped in foil. Even if a very tiny amount of light, may want to use something to create shade on it. So you made the salt, added 2,4 pentanedione (acetylacetone), with your additional acid helping the reaction in a few minutes. You then neutralize with KOH, which precipitates your product. Do your cannula filtering under your inertness, then heat it to 60 c, with vacuum. Add distilled water and filter again.

Advanced chemists would use a filter stick, but if you knew what one was, you probably wouldn’t need this book. Then to isolate your product dissolve in DCM and precipitate by adding ether until it precipitates and cannula filter, The reason is no reaction is 100%, and any unreacted or byproducts would be in there, and they need to be removed. If you have chloroform handy, it can be used for this precipitation instead of DCM, if you prefer. The azide method also starts with making the HCL salt. This method is an ionic reaction, and you need to keep the temp really low, as at a slightly higher temp, an entirely different reaction occurs. Which means you need to keep adding ice to ensure it stays low that temp. Aqueous baking soda precipitates it, but you can extract with ether as your calcined potassium carbonate will aid to dry it with your amine. They may have used ether to extract as perhaps they were lazy or ina mad rush. Your reagents should be prior cooled to close to freezing to begin. The azide according to patent is supposed to be yellow. Now the azide method has a very serious drawback, which is - no matter what configuration you start with, it will result if your amine calls for it, an active product as a component, meaning psychoactive. God is on your side on this one, to keep you alive, as hydrazoic acid is extremely poisonous, as the potassium carbonate will neutralize it and any excess amine will complex with it, and even though many azides are explosive, this one isn't, so you will be alive to possibly account for any legal matters. Read the legalese chapter carefully. To calcinate it, you heat with a high temp flame until a change occurs.Back to your pyrazole clean up. If you used a dialkyl amide, it is simple to add distilled water, to extract out the dimethylpyrazole, if a mono alkylamine was used, you need to heat to a temp about 110 c, and use a strong vacuum perhaps a two stage to remove it. Those can be loud and may attract unwelcome attn, Dimethylpyrazole is indeed a poisonous type molecule and has to be removed. One day, if you ever keep your freedom long enough, if you ever advance to doing column separation with a salt, sometimes that actually separates things. A view of the azide method, it uses sodium nitrite, to form nitrous acid in the reaction vessel to convert the hydrazide to the azide. US patent 3346580 shows some molar amounts etc. for carrying this out on a slightly different molecule, If you scour and search online enough, you can find some exact recipe details and amounts etc, The azide patent US patent 2,438,259 mentions using acetone to crystallize the iso, and acetone dissolving the regular, with adding ether until it precipitates. It also mentions another method to form amides, by adding your amine dissolved or mixed in ethanol at a cold temp, then slowly raising the temp to slightly above RT, and continuing for about an hour. A later chapter will have the only method I would advise to convert iso to regular, that way you do not have to keep doing tedious precipitations and fractional crystallizations again and again, or dump tons of things down a column and hope it all separates, “So I thought it was high time (a pun?) that Sandoz resumed chemical research on ergot alkaloids, unless we wanted to risk losing our leading role in a field of medicinal research, which was already becoming so important.” “Professor Stoll granted my request, with some misgivings: "I must warn you of the difficulties you face in working with ergot alkaloids, These are-exceedingly sensitive, easily decomposed substances, less stable than any of the compounds you have investigated in the cardiac glycoside field. But you are welcome to try." Hoffman,“Claims that LSD may easily be prepared, or that every chemistry student in a half-decent laboratory is capable of producing it, are untrue. Procedures for synthesis of LSD have indeed been published and are accessible to everyone. With these detailed procedures in hand, chemists would be able to carry out the synthesis ...in order to produce stable preparations, however ... not easily acquired specific experience are required, owing (as stated previously) to the great instability of this substance.” Hoffman. Anyway, if you scan his book, you will see he did have a fume hood, but initially they denied his request to have better stuff, so had to work with benchtop things at a microscale, like fractional precipitation, and fractional crystallization etc. The column didn’t come, he said until much later, and his precursor although requested from his boss, Stoll, after having approved to work on the alkaloids,

when asking for half a gram he was refused, and had to import ergot from Spain or Portugal to get started.
So example 3 in the patent would be preferred as you don’t need potassium carbonate, don’t have to keep shaking it, and will complete faster. To get it to minus 5 C, that is the exact temp of benzene in dry ice; alternatively, plain ice with NaCL. It may take some practice doing an ice salt bath, then once cooled, allow it to warm to room temp, once there let it run for 90 minutes. At that temp the alcohol solvent does not react with the acyl azide. It is the original Curtius reaction before he found out what happens if you heat it. If you did, you would find out too, and it would destroy the lysergic skeleton. The excess amine complexes with the hydrazoic acid, so you can pull it into a container and use nitrous acid to break it down. Example 6 of US patent 4101552, shows the sodium nitrite lysergic azide method.

CHAPTER 3 ALKALOIDS AND AMINES ‘Your basic dialkyl amine can be had, made, or obtained in a variety of ways. Reducing acetamide can make your ethylamine, further introduction to your molecule can add another ethyl group. One option is an ethyl halide, like bromide or iodide. From insect repellent DEET with the alcohol catalyzed alkaline hydrolysis is another poorer option, Oftentimes, the salt of the amine can be had, which is easier to transport. But that is not the amine I am wanting to type about in this chapter, For a variety of reasons, a mono alkyl amine would be in some respects and instances, a better choice. Luckily, there is one, which opens up some other possibilities on this topic. There is of course a minor drawback, It comes in two forms an Rand an S, Luckily, there is a simple procedure most could carry out to get the desired enantiomer. 2 Butylamine can be separated and isolated with good enantiomeric excess. If attached to the lysergic skeleton, and chromatography employed, the R (the desired amide) comes through first, so knowledge of that could help any serious experimenter. You need to add your 2 butylamine in ether to tartaric acid to form a one to one complex. Recrystallize in dry ethanol. The mother liquor from the first precipitation contains mostly R,and alittle R, The precipitate from the first is subject to a second crystallization, what precipitates is pure S, the mother liquor contains mostly R, more % R than the first mother liquor, but far less of an amount.
If desired one could combine the two mother liquors, or use the smaller amount of the R from the second which has a higher purity %, either way render alkaline in some water and distill, then dry and distill and prepare for final drying. Amines need to be stored properly, and that one isa very fine amine to have. MEK resembles it in the carbon chain, with an oxygen instead of a nitrogen at that spot, it is also called sec butylamine.Alkaloid sources, so many, and so many ways. I will mention several, but there are more. Among natural sources are ergot, woodrose seeds, and morning glory. The typical first step for those is to grind them thoroughly. If a smaller amount an electric coffee grinder can work, for larger amounts, a decent blender that gives a similar type grind can be used. Sometimes you have to shake those a bit to get it all ground up good. Usually, a defatting step is used, that can be done in two ways, one is to heat the solvent used for that, add it to the seed that was pulverized, and continue keeping it hot for 30 minutes, then separating it from the seed mush, to be potentially re-used for future defatting once distilled. The other way is to soak it for 2 days at RT. Either way, once the aroma from that solvent has gone, it is ready for an extraction tech, If using the hot defatting step, do not exceed 30 minutes hot, as you can start to pull alkaloid into it at that point. Solvents close to hexane can be used for that. The standard extract is to freebase the alkaloids into a solvent that solvates those alkaloids in that form, So you can already see what the issue is with that. To minimize degradation, or decomposition, guess how you do it? You will put some cotton at the bottom of your addition funnel, with some filter paper covering that, and load your dry seed mush into it. Run your inertness into that, and fill your extraction solvent into that. There are several ones, usually trying to get the alkaline extraction to work with an organic solvent. Once you have it set for a good hour, lower it into your

receiving flask with inertness. Add a little more extraction solvent to your addition funnel, just near the bottom, and shine your dim blacklight on it to see if any significant fluorescence is there.

If that is the case fill it up one more time and let it soak, if not lower the little bit to add it the other. Now you pull it out of there by cannula to a reaction vessel that has an addition funnel at top. You can proceed on the extraction steps at that point. You proceed to make it acidic and separate, and make it alkaline and separate back and forth until you get it either to your desired base or acid salt you want. If going back and forth between ether and water several times, you may leave clavines behind, and preferably carry carbonyls through to the next stages. Now, if using ergot or morning glory (pref. heavenly blue) there is another tripeptide still in the seed mush, not in woodrose. To follow up on that, the extraction is 70 ml acetone, 2 grams tartaric acid, with the rest being distilled water until 100 ml is reached. That pulls ergosine out of the ergot or morning glory as the salt.If not having access to inertness, and a more experimenter type idea, is after defatting once ground, use 70 ml methanol (or even ethanol) with tartaric acid in water until 100 ml is reached, to pull the little LSAs from seed out. Make sure you always keep it in salt form. Before you shake it with your standard solvents for freebase alkaloids to try to clean it up, first distill off (if a water aspirator can be had that would help) the methanolor alcohol. Then remove the water part (recall to keep it dim lighting, especially when working around excess acid in water or alcohol) and attempt to recrystallize from ethanol or methanol, heat it up, add it to your extract to just dissolve, allow to cool slowly, and shove in the fridge; if you get some crystals, filter properly, 2 or 3 mg assay, to see if any tinge effects, and even running down a column as the salt, recall between 1 and 5 % of the alcohol solvent used being another solvent may help retention if pure dry alcohol can’t fully separate them. Use a long burette for it, and keep bubbles out of the column while loading. Use the blacklight sparingly after it drips for a while to start to spot your desired product. A smaller amount of solvent may yield further crystals from the mother liquor contents upon recrystallization. Now the ergosine salt can be recrystallized, or run down the column, or run through your inertness procedures, the freebase is not able to be solvated in water so that can assist cleanup, then put it into either freebase and salt form for your desired experiments or reactions. Now the DEA says morning glory seeds have never been found to be a successful source for LSD manufacturing, but maybe a serious experimenter may prove them wrong. Usually, the cheapest tripeptide on the world market can be had for between 10 there are pharmaceutical sources also in small quantities. and 20 dollars per gram in quantity, but I shouldn't go into all that, There are several books on this topic, and I have at least scanned most of them, but one I bought a few times back in the 90s and re read while in college was by uncle fester. In there he mentions spraying a field of wheat or rye with ergot fungus to grow ergot, which was the original way Sandoz did it. That could work, but worries about it spreading are a no no. If on wheat, ergocristine dominates as the alkaloid, if on rye, ergotamine. You should get his book, as it is filled with jokes, and I heard he came out with a third edition, where people forced him to put phosphorus chloride method in it by arm twisting, but since he is usually known for meth type things, in a Sandoz patent it mentions in passingphosphorus triiodide as a method. My advice would be to form it in a separate container and add it to the vessel; that would be one he could detail in his next edition, if someone knows him or how to contact him. There is a strain of claviceps that works for liquid culture, called paspali Stevens and Hall. That strain could be acquired. You have to use sterile tech, a clean room, maybe a HEPA filter and spray Lysol crazy ahead of time and maybe even work in a box for transfers, and be cleaned up good yourself, from petri to oxygenated shaker flasks and then stirring fermenters; serious researchers could look into it, and the small LSA types it makes are in the liquid, not the mycelium for extract. It would be pricey. If you find some ergotamine pills that have caffeine in them, usually those are tough to separate easily. One way would be after warm water to pull it out of the pill junk, then removing the water, using cold water several times to try to reduce the amount of caffeine. Another way would be to try to sublime out the caffeine. If you can remove a lot of the caffeine, maybe a column runas the salt could help. Don't put your blacklight up close to what you are checking, keep it at a distance to minimize degradation.

CHAPTER 4 SO3 ...WITH A TWIST

This method is really old school, but I would advise it should be retired. I present it here for historical purposes. First off you have to freebase the lysergic you have, in order to form the metal salt. The traditional $03 method has one mole going to the nitrogen in the top ring also. Plus the cleanup requires a molecule that is not good for the environment, and could be cancelled worldwide in the snap of the fingers, and you have to also salt it out to even hope you get it out of the reaction mixture. Anyway, once you form the metal salt, I advise a different approach anyway. It is an old school chemistry trick that old chemists know, and would be a better choice; after freebasing it and making the metal salt, might as well have a synthesis procedure. Usually, if you want to add to the one spot, it takes certain conditions, so that isn't a real worry with this method. The method is called direct anhydride formation. Usually, the amine may prefer the stronger acid in mixed anhydrides, but it is likely some amine would join to the lysergic. The advantage is, since not working with the monohydrate, you won't need a tertiary base to get it to work. DCM will work for the solvent, and hexane added and removed should ensure it is dry enough to proceed. Acetyl chloride will form the direct anhydride practically quantitatively one to one. Prep chem shows how to make acetyl chloride and acetic anhydride, from oxalyl chloride. So the acetyl chloride forms salt and the direct anhydride in high yields. The synthesis process will be detailed in the anhydride chapter.If some insist, just pull copper out of your wall, add sulfuric acid to it, with hydrogen peroxide or nitric acid, to make copper sulfate, and heat it and run the $03 into DMF, but again, I do not advise anyone to do such things. To make lysergic the freebase you need to put the salt into your inertness vessel, add DCM, stir a bit. Then add ammonia water, and stir, stop stirring, do the separation. Remove the ammonia water from your addition funnel. Now add regular distilled water, and stir, and stir, and stop. Now pull it out and back through and separate the DCM back in, check the water with your blacklight and see the lysergic has gone into it. You can move the water with lysergic freebase from your addition funnel, into your container for drying to the monohydrate and prepping for the reaction, again pyridine will be able to transfer it in once your reaction is prepared. If you weigh that container ahead of time, then move in your lysergic and prep it, you may get the weight for calculations for the metal salt, as you can weigh it when ready and subtract, Using the direct anhydride method, being ballpark will be good enough, exactness is not as pressing as the $03 reaction. So prep your vessel like the pocl3 method, and get ready to form your metal salt. You are going to use hexane once the metal salt is formed, to ensure dryness, and the reaction proceeds like in the anhydride reaction chapter from there.

CHAPTER 5 CDI CDI is water sensitive, so prep as such, Which, as you found so far, is to your advantage, actually. It will work with the monohydrate. This is really straightforward and clean, Just use a little extra cdi, When I looked at this reaction in detail years ago, I noticed, due to it being so clean, you could rewrite the cleanup to isolate the salt, if desired, The imidazole could be recovered, and if you ever develop the nads to work with phosgene if holed up for a bit, could regenerate it for some time. Notice where everything goes in different solvents, the stronger acid will be attracted to the stronger base, and if careful with the lighting despite some excess acid in water or alcohol, could work with that either as the salt down the column or repeated crystallizations, or you could do it the usual way they write them up with the base, Depends how serious you are about work and how good one is at protecting that double bond, Perhaps synthesizing a small amount of imidazole couldn't hurt to keep you there for a little while longer.

CHAPTER 6 ANHYDRIDE

This was one of my favorite reactions since I read the cookbook back in the late 80s or early 90s. It can be done in DCM, it works with the monohydrate if using an excess of anhydride, the reaction basically works itself and has the clean up as a breeze. In fact, it could be used by an engineer for a massive scale up with timers and pipes and things engineers do, TFA, the acid precursor in theory, is widely used in industry; I don't know if anyone has ever found an easy way to dehydrate it or not. If you use it on the monohydrate, you need a tertiary base to complex with that so your amine can get to it fine, just use slightly more TFAnhydride. If your two stage vacuum can pull 1 mm, it will remove that water of crystallization at just more than 100 C, At 2mm, it is 140 C, so the salt would be preferred, to keep it stable if heating at that time and temp. I will go into the cleanup on this, so you can see the process after I outline the reaction sequence, This one is someone's baby, if that someone could ever get their hands on a bottle of the anhydride. Since trifluoroacetic chloride is a gas until you get it super cold, any attempt to form it would have to be done way cold, below -40 C. Dry ice and acetone can get way colder than that. In theory oxalyl chloride, or thionyl chloride, may chlorinate it, if so, if more TFA is added, might form the anhydride, or maybe even the metal salt of TFA. Who knows? So the iso, once isolated by itself as the freebase, just needs ammonia in anhydrous ethanol like Shulgin in chapter one that I told you not to do. First pass gets it to around 90%, some fresh ammonia in ethanol gets it to quantitative, so there is nothing else to worry about; so if you did not do that in part one, you only have to do the ethanol thing once instead of twice. I will tell you the only acceptable procedure; some guy postingon science madness board showed how to properly put dry ammonia in, but he did it in methanol. It starts with an ammonia salt to generate dry ammonia gas, which will be bubbled into your dried ethanol, which gets it at RT to about 15 or 16%, more than sufficient for the isomerization / epimerization to occur. So you put your items prepared under dry inertness with your dry solvent into the freezer to get to the correct temp. Then transfer one into the other and put it back in the freezer. Then bring it back out of the freezer and transfer into your prepped amine container for the reaction. The rest of the procedures are done in tedious fashion as in the other methods. Just follow the directions. One important note for an engineer wanting to scale this up to industrial or factory conditions. If a solid residue ever has amine salts in it, it may be temporarily protected from atmospheric attack. If you follow other methods for iso to regular, you have to form the salt then, then either recrystallize knowing the iso will be in mother liquors mostly, or run it down a column as the salt. Keep lighting severely restricted due to excess acid.

CHAPTER 7 PEPTIDE COUPLING AGENTS — PYBOP

So this one is rather incredible actually but you have to have a tertiary base. It is used in biology circles for putting together amino acids, and due to its unique electronic nature, can put amino acids together in even 4 or 5 % water. You need to keep things dry to work with the hydrate, the anhydrous form of lysergic will give initial higher yields, but since it is simpler working with the hydrate, and the ease of recovery of unreacted, I advise to work with the hydrate. Because of some items in this, when the ammonia stirring is done, some goes into that layer, and will need to be extracted back out, so you need another reaction vessel prepared if you want to get that product back. So the ammonia wash and separate by the procedures I showed, that other reaction vessel you send it to you need to use DCM to extract that back, send back to your addition funnel after stirring, use a blacklight to check and verify that is indeed the case, and then follow the order of washings, the regular distilled water layer has the unreacted lysergic, so transfer that out to be made back to a salt for prep for later reactions, the salt water or brine it is called helps to rid some of the ionic items from the reagent, and may even dry a tad, then your drying as I detailed in a previous chapter and it is cleaned up in the manner you choose comfortable with. Sometimes other alcohols can work to form the salt, but you should stick with typical ones to gain familiarity before experimenting. Purify this one good, as you don't want residue from that coupling in your product. I hear DCM from the bottle can be used, so that simplifies the procedure. Because of this, if using this method, the chemist forced as a friend of a biker may not have to cannibalize their distillation unit.

CHAPTER 8 ESTERS AND ENZYMES

One of the methods seldom mentioned or used is quite known and taught, as carbonyls are always looking for things to replace what it has attached to it, and vibrates millions of times per second looking, It follows a certain order and as luck would have it, amides are preferred ever so slightly over esters. That means if you have an ester, oftentimes if an amine is nearby, it would swap it out by carbonyl default, Such a reaction would need to take place in a solvent, and having it slightly elevated in temp would get it to happen slightly faster if it is going to. Too high of a concentration of amine may isomerize it, and that iso formation would proceed and get worse with more time. The most straightforward way, just to demonstrate the concept to you, really just for a prep at the benchtop and not a manufacturing method, due to its dangers, is diazomethane. It is a trivial procedure at small scale, and is easily done by pipette in ether, with a color change and something to back it off to neutralize it. Just form the methyl ester on the lysergic sulfate salt. That is not for manufacturing due to its dangers, only for a one time small scale bench prep to let you see that it does indeed work. So you add in ether, watch the color change, wait a few seconds until the color change goes away, add a little more, wait until the color change reverts, and keep adding like that incrementally until the color change does not go away. Then back it off with a small carboxylic acid to remove the color to neutralize.Okay, now on to what to do with small seed type LSA salts. Because they are small amides two, three or four carbons, that ever so small difference between the order of reactivity on carbonyls can be exploited. Convert the small amides to esters, so you can then do the correct order. The normal, usual order in case you already forgot, is ester to amide. US patent 45242084, also a European patent has it, EP0095092A2. Example 1 is using dry hydrogen chloride gas, at a cold temp, to effect the esterification of small seed type LSA’s. It works with the salt. The stronger HCL will displace the current salt, but the advantage is it does not require inertness, but only dryness. It puts it in cold, and warms it up, as that may reduce the amount of dissolved gas. Then it cools it down to crystallize the rest that hasn’t already, and adds cold ethyl acetate to finish the precipitation. This is where serious experimenters come in. You have some options to try not to destroy your compound, as it most likely still has plenty of HCL in it, and any significant water will most likely destroy your item. One could try to dilute it with cold dried methanol and swirl it around and try to vacuum it out. Or find a way to try to pull it out. Or you may think you are fast, and can try to quickly filter it by a vacuum filtration with cold methanol standing by. Experimenters will figure it out, I am sure. If you added, you will have to do a recrystallization again to isolate it. Be aware, the ester is not as stable as the other compounds despite being a salt. You have about half a day to a day to do whatever you intend with it, like a melting point test. A less pure inert gas would be fine to achieve dryness, or other gases just send it through several drying stages first and use a drying tube perhaps with cotton to prepare your vessel for your attempt to drive in dry HCL. One may also try a vacuum with drying in between the vacuum source and the flask to try to pull it through from regular air dried en route and turn it off and repeat trying to flush it out several times. Also, a needle may slide between a rubber stopper and your glass, just flame dry the needle and draw dry gas into it and expel in the atmosphere and repeat 3 or 4 times to dry to add solvent. Dry ice and acetone can get it that cold, use a real thermometer, and add or withhold dry ice as needed to get the correct temp called for. The next advance is a very unique way to try and form the ester from the small amides from seeds. There is an enzyme papain from papaya that is known as a hydrolase. There are about 3 or 4 other kinds of enzymes that will do the same type thing, they have different name types, even though capable of doing the same thing for this purpose. Many have cofactors or coenzymes, but this one is widely available, stable, and does not require any of those. At pH 9, basic conditions, it favors esterification over amidation by a thousand fold. But at basic conditions, that would require inertness.

So a serious experimenter would try it at neutral pH, pH 7. Conveniently, that can be tried in a test tube. It may still favorforming the ester, so 40% alcohol in water with the enzyme to effect the transformation might do the trick. If one is desiring to try the fabled transamidation reaction with it, know that nature does not work with dialkyl amines, only mono alkyl amines. I would reduce the % to around 20% amine, as Mother Nature does not worry about water for these reactions as chemists do. Too high of a concentration of an amine may favor isomerization, which one wants to avoid to avoid needing high purity inertness. Another enzyme is chymotrypsin, it needs trypsin to activate, and it is a proteolytic enzyme, which is available, but works closer to pH 7. Perhaps a graduate student can do research on this aspect, and find enzymes that convert to the ester at pH 7 or below, and or even convert the ester once formed back to amide at neutral pH. The standard way is the ester salt, either suspended or dissolved in a solvent, with stirring, and an amine of not too high of a concentration with the temp elevated slightly for a few hours, The dialkyl amine is a weak base, so the lysergic will indeed stay a salt.CHAPTER 9 TOTAL SYNTHESIS When the US government wanted to flood the water supplies of the USSR to be able to temporarily incapacitate their general populace if needed, they also wanted to protect their own water supplies in case the Russians wanted to do it back, so they needed tonnage quantities of LSD, of course. So they put the resources of the nation at their disposal, and quickly found a way to do it. Of course by the time they realized it was only stable for a few years, once they already had a few hundred pounds, they abandoned making it and stockpiling it. But, they discovered a way to do it, There was an improvement to their method; that improvement makes it possible to synthesize from scratch, The author was named Moldvai, the title of the research was ‘Enantioefficient Synthesis of Ergocryptine’. The US government method used a reduced indole, an indoline (the pyrrole ring not having a double bond in indole, the non benzene section) and used functional group swapping at the top part, at one point even they switched to TOSMIC at their synthesis site, to avoid HCN in the handling of the reagent. That reduces the number of steps at the end. The improvement protects the indole from the first acylation using the PIV protecting group. They recover the protection at the one spot to reuse and recycle. I will explain the outline of it so you can understand. Get the paper handy and read along to learn how a synthesis from scratch happens. With a cheap precursor, which in quantity gets even cheaper, they use the standard acylation to close the first ring, with indole intact from the aluminum trichloride sterically blocked by the PIV protecting group. That has to be anhydrous to work. You have a certain order of protection, deprotection, it is vital to follow the order, so study the paper closely. They prepare the special amine in a pressure cooker; that is in example 3 of patent 2809974A. That is just a halo acetone, protected by the method you protect ketones normally. If you notice the nitrogen in the topring, it is just an acetone to get to the double bond. In the procedure of the paper, the experimental part, you see how they make that googley eyed funny looking thing; that is just the ketone protected by a glycol, which is deprotected by acid, So you add that amine to the brominated molecule at that part to have the simple part to make the top ring and close with a lithium salt in the presence of a tertiary base. There have been bromination procedures since that paper came out that have a slightly higher yield, So you close the first ring, add your acetone made amine, and close the top ring, You have the lysergic skeleton. Protect, close the first ring, halogenate, add the part, and close the top ring. Close the first ring, close the second top ring. They need to then lengthen the carbon chain, at the top ketone, by cyanide, via TOSMIC, and then to the ester. You have to follow the proper order of protection / deprotection, and you got it. That brings up another potentially important advance about this.

You know how to protect ketones now. They resolve the ketone lysergic skeleton, as when you close the top ring that decides if it is dextrorotary or levorotary, so they resolve it at that point. If you recall, the hydrazine hydrate reaction makes racemic. But that is not from the reaction mechanism itself, but from the conditions of the reaction. If you start with dextrorotary, subject to hot hydrazine hydrate for a length of time, it will make D and L. If you start with L, and subject it to racemic conditions in hot hydrazine hydrate for a certain time, that will make D and L.

There will be some losses, but it is not a total loss is my point, If that protected ketone dissolves in hydrazine hydrate, either as salt or base, it can be racemized again, and subject to a further resolution. TOSMIC can be made if need be, but it is fairly cheap, but can be made cheaper, if doing this stuff, you got the skill easily to do such. The free HCN generated when making it into the ester could easily be handled at that point if getting to this point in life to have to resort to such things as this to begin with, if it has truly really come to that.

CHAPTER 10 THEORETICAL AND ALTERNATIVES

For those not wanting to wade through the realities of the legal issues about this, and wanting more than just the accurate information finally being disseminated, there are lesser ways to experience such a thing, Example, if fresh ‘shrooms are had, drying in a jerky maker at a low heat setting, grinding up in a coffee grinder once dry, extracting with hot ethanol, filtering out the ‘shroom mush, and recrystallizing should produce crystal psilocybin. San pedro cactus, an acidic extraction, basifying and then re-acidifying in the sulfate salt form will allow recrystallization to be uniquely isolated for accurate weighing. Or morning glory seeds washed and dried, ground, and subject to a water extract, can do the trick. DOC is a close approximation, but now the US wants to move it into schedule 1. Carbonyls are indeed highly reactive, if a small LSA salt can be had, if an amine is put near it, even ina solvent, it may in along time, might swap it out, if it is finicky towards it. Too much amine concentration might isomerize it. If anhydrous lysergic acid salt, is put in a solvent with an amine salt, and heated, it may drive off water, the maximum yield would be 50%, as the water spit out might go to the dry acid to make it the monohydrate,which would not further react. You would have to basify it, to get the salt off the amine. There are places in the world market, where various molecules can be had, as some countries do not care about certain laws, it would just be being able to get whatever it is from somewhere and sent to where you need it to go, either the items themselves, or items close to it, Electromagnetic communication would be shunned, and snail mail procedures employed. Mail forwarding services in various other countries, to open and resend in a different envelope to communicate back and forth, and traveling to where it is picked up, and your responsibility to get it to where it needs to go. Manufacturing then, would never need to occur, just buying or procuring it While writing this book, a new patent was released of a new method using a phosphorus anhydride ina solvent of ethyl acetate, WO/2022/008627 describes it using propane-phosphonic acid anhydride (T3P).
It is possible to form the methyl ester with anhydrous lysergic acid salt, using the methanol with dry HCL gas dissolved in it. It would take acouple days at room temperature at around 4% HCL, and it forms slowly enough to where the water spit out would be small enough to get captured by another dry lysergic molecule to where it would not have the pH to destroy it, in theory. A small amount would be for the test. The lysergic hydrate salt formed would predominate, and so would likely precip out when going to isolate it after removing the excess HCL. The ester formed would be in the mother liquor; a melting point test could determine it; the ester melts at a lower MP. A potential engineering way to obviate the requirement for inert gas during the alkaline hydrolysis: fill the container completely with slight overflow and close it off to do your reaction, A connection between them below that level would allow them to mix when needed, a valve of some sort. To benchtop it, in an unusual way, is to have a 3 neck flask where the necks are level. Your KOH addition funnel has an additionalfunnel attached above it, the same for your sulfuric side. You fill up your reaction vessel just past the ptfe stopcock with your alkaloid salt. You can either heat ahead of time then close it off, or heat afterward, Then open the KOH stopcock, to allow to mix. The upper KOH addition funnel just has enough above the stopcock where it is closed off. Might want to cool your sulfuric, you must have stirring going good. Once a salt, you are okay as long as you keep it cold. If you can't bench top this, you know what you need to build with valves, to potentially get this without inertness. It is taking medium scale, and trying to get it at the benchtop prep level, reverse chemical engineering.

Now that a method of improvising the procedures has been shown, some may want to improvise certain procedures themselves. Trying with needles hooked in some fashion to PTFE tubing of who knows what. Chem flex may also sub for cannula transfers perhaps and others are ingenuous and possess the trait of ingenuity; who knows?

CHAPTER 11 LEGALESE

This book is written in accordance with free speech protections and is for informational purposes. It is the responsibility of the reader to ensure they are in compliance with whatever laws of whatever jurisdictions they may be subject to. The US government has a system of several layers of enforcement for various items in place, and no US citizen should ever break the laws on this topic, as if the government had any secret capabilities, they may apply those to this topic. You have been warned. So far, the DEA has been batting 1,000 on this, which really stands out like a sore thumb with their resume on everything else the last two generations. I know some won't listen, and I am not responsible for those actions. If anything, the DEA is, as all they had to do is stop their intrusion, and I would not have published; that is on them. So the remainder of the world can thank the US DEA. There are places world wide where some may do this; if even a few hundred or even a few thousand were to, and were successful, there would be more than there has ever been, if the amine choses was the diethyl, with the exception of when the US government did it, of course. My surmising tells me the DEA will no longer have the batting average they used to on this, and in about 2 years, the people of the United States will modify federal drug policy anyway. ‘Michael Yost